(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2002 (22.08.2002)

PCT

(10) International Publication Number
WO 02/064142 A1

(51) International Patent Classification[7]: A61K 31/47, 31/505, 31/135

(21) International Application Number: PCT/EP02/01248

(22) International Filing Date: 6 February 2002 (06.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/268,839 15 February 2001 (15.02.2001) US

(71) Applicant *(for all designated States except US)*: **JANSSEN PHARMACEUTICA N.V.** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **END, David, William** [US/US]; 1530 N. Fiedler Road, Ambler, PA 19002 (US).

(74) Agent: **DE CORTE, Filip**; Janssen Pharmaceutica N.V., Patent Department, Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/064142 A1

(54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH ANTIESTROGEN AGENTS

(57) Abstract: The present invention is concerned with combinations of a farnesyl transferase inhibitor and an antiestrogen agent for inhibiting the growth of tumor cells, useful in the treatment of cancer.

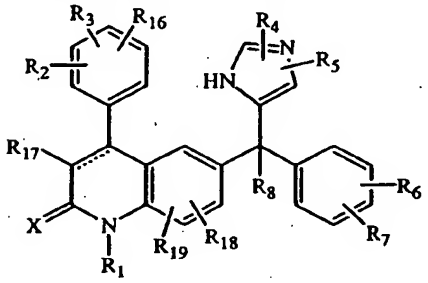
FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH ANTIESTROGEN AGENTS

The present invention is concerned with combinations of a farnesyl transferase inhibitor and an antiestrogen agent for inhibiting the growth of tumor cells, and useful in the treatment of cancer.

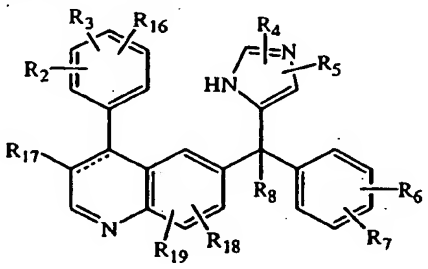
Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer. A particular group of oncogenes is known as *ras* which have been identified in mammals, birds, insects, mollusks, plants, fungi and yeasts. The family of mammalian *ras* oncogenes consists of three major members ("isoforms") : H-*ras*, K-*ras* and N-*ras* oncogenes. These *ras* oncogenes code for highly related proteins generically known as $p21^{ras}$. Once attached to plasma membranes, the mutant or oncogenic forms of $p21^{ras}$ will provide a signal for the transformation and uncontrolled growth of malignant tumor cells. To acquire this transforming potential, the precursor of the $p21^{ras}$ oncoprotein must undergo an enzymatically catalyzed farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Therefore, inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, will prevent the membrane attachment of $p21^{ras}$ and block the aberrant growth of *ras*-transformed tumors. Hence, it is generally accepted in the art that farnesyl transferase inhibitors can be very useful as anticancer agents for tumors in which *ras* contributes to transformation.

Since mutated, oncogenic forms of *ras* are frequently found in many human cancers, most notably in more than 50 % of colon and pancreatic carcinomas (Kohl et al., *Science*, vol 260, 1834 - 1837, 1993), it has been suggested that farnesyl tranferase inhibitors can be very useful against these types of cancer. Following further investigations, it has been found that a farnesyl transferase inhibitor is capable of demonstrating antiproliferative effects *in vitro* and antitumor effects *in vivo* in a variety of human tumor cell lines with and without ras gene mutations.

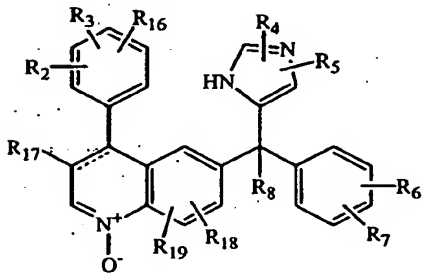
WO-97/21701 describes the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting (imidazoly-5-yl)methyl-2-quinolinone derivatives of formulas (I), (II) and (III), as well as intermediates of formula (II) and (III) that are metabolized *in vivo* to the compounds of formula (I). The compounds of formulas (I), (II) and (III) are represented by



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9, wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy,

Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or

when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1), or

-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, or a radical of formula

-O-R^{10} (b-1),

-S-R^{10} (b-2),

-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino,

C_{1-6}alkylcarbonylamino, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

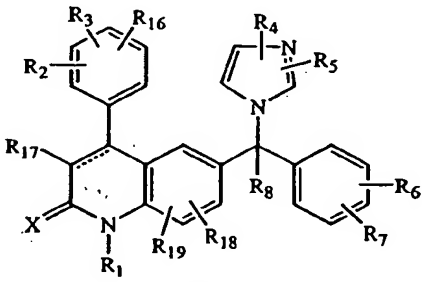
R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{19} is hydrogen or C_{1-6}alkyl;

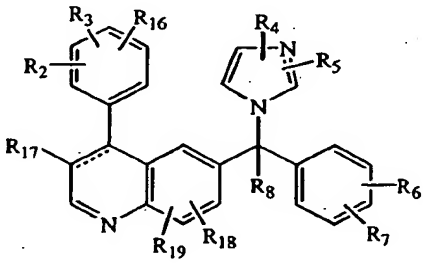
Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.

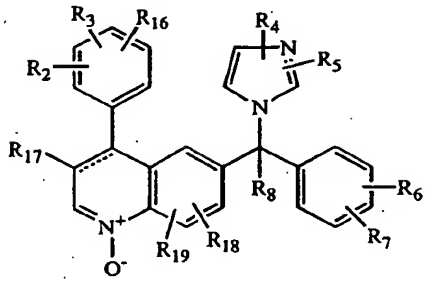
WO-97/16443 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IV), as well as intermediates of formula (V) and (VI) that are metabolized *in vivo* to the compounds of formula (IV). The compounds of formulas (IV), (V) and (VI) are represented by



(IV)



(V)



(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,

or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9,

wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, amino-C_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, Ar^1, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkyl$S(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy or Ar^2oxy;

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxycarbonylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, Ar^1, Ar^2C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl;

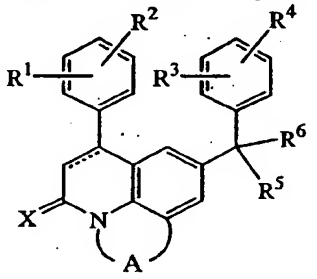
R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{11} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo;

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.

WO-98/40383 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VII)



(VII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

-A- is a bivalent radical of formula

-CH=CH-	(a-1),	$-CH_2$-S-	(a-6),
$-CH_2-CH_2$-	(a-2),	$-CH_2-CH_2$-S-	(a-7),
$-CH_2-CH_2-CH_2$-	(a-3),	-CH=N-	(a-8),
$-CH_2$-O-	(a-4),	-N=N-	(a-9), or
$-CH_2-CH_2$-O-	(a-5),	-CO-NH-	(a-10);

wherein optionally one hydrogen atom may be replaced by C_{1-4}alkyl or Ar^1;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy,

C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^2, Ar^2-C_{1-6}alkyl, Ar^2-oxy, Ar^2-C_{1-6}alkyloxy; or when on adjacent positions R^1 and R^2 taken together may form a bivalent radical of formula

-O-CH_2-O- (b-1),

-O-CH_2-CH_2-O- (b-2),

-O-CH=CH- (b-3),

-O-CH_2-CH_2- (b-4),

-O-CH_2-CH_2-CH_2- (b-5), or

-CH=CH-CH=CH- (b-6);

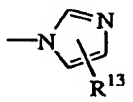
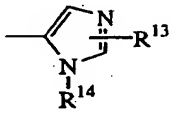
R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^3-oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R^3 and R^4 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1),

-O-CH_2-CH_2-O- (c-2), or

-CH=CH-CH=CH- (c-3);

R^5 is a radical of formula

 (d-1),  (d-2),

wherein R^{13} is hydrogen, halo, Ar^4, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxy-carbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{14} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^6 is hydrogen, hydroxy, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^5, Ar^5-C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^7 (e-1),

-S-R^7 (e-2),

-N-R^8R^9 (e-3),

wherein R^7 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^6, Ar^6-C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

R^8 is hydrogen, C_{1-6}alkyl, Ar^7 or Ar^7-C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^8, Ar^8-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^8-carbonyl, Ar^8-C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

wherein Alk is C_{1-6}alkanediyl;

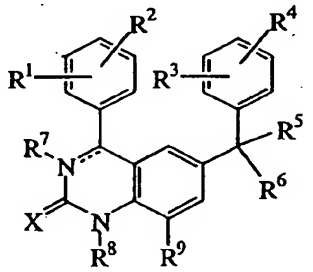
R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^9 or Ar^9-C_{1-6}alkyl;

R^{11} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^{10} or Ar^{10}-C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, Ar^{11} or Ar^{11}-C_{1-6}alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

WO-98/49157 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VIII)



(VIII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or

di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^1C_{1-6}alkyl, Ar^1oxy or Ar^1C_{1-6}alkyloxy;

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl or trihalomethoxy;

R^5 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

$-O-R^{10}$ (a-1),

$-S-R^{10}$ (a-2),

$-N-R^{11}R^{12}$ (a-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^1carbonyl, Ar^1C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

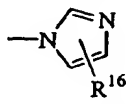
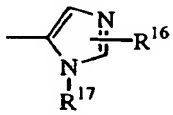
wherein Alk is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^6 is a radical of formula

 (b-1),  (b-2),

wherein R^{16} is hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino,

C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl,

C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^7 is hydrogen or C_{1-6}alkyl provided that the dotted line does not represent a bond;

R^8 is hydrogen, C_{1-6}alkyl or Ar^2CH_2 or Het^1CH_2;

R^9 is hydrogen, C_{1-6}alkyl , C_{1-6}alkyloxy or halo; or

R^8 and R^9 taken together to form a bivalent radical of formula

-CH=CH- (c-1),

-CH_2-CH_2- (c-2),

-CH_2-CH_2-CH_2- (c-3),

-CH_2-O- (c-4), or

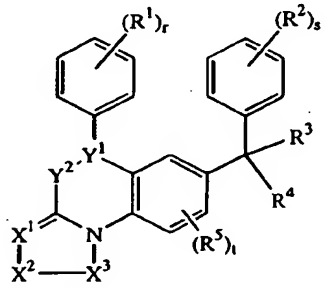
-CH_2-CH_2-O- (c-5);

Ar^1 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl;

Ar^2 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl; and

Het^1 is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

WO-00/39082 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IX)



(IX)

or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$=X^1$-X^2-X^3- is a trivalent radical of formula

=N-CR^6=CR^7-	(x-1),	=CR^6-CR^7=CR^8-	(x-6),
=N-N=CR^6-	(x-2),	=CR^6-N=CR^7-	(x-7),
=N-NH-C(=O)-	(x-3),	=CR^6-NH-C(=O)-	(x-8), or
=N-N=N-	(x-4),	=CR^6-N=N-	(x-9);
=N-CR^6=N-	(x-5),		

wherein each R^6, R^7 and R^8 are independently hydrogen, C_{1-4}alkyl, hydroxy, C_{1-4}alkyloxy, aryloxy, C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, cyano, amino, thio, C_{1-4}alkylthio, arylthio or aryl;

$>Y^1-Y^2-$ is a trivalent radical of formula

$>CH-CHR^9-$ (y-1),

$>C=N-$ (y-2),

$>CH-NR^9-$ (y-3),or

$>C=CR^9-$ (y-4);

wherein each R^9 independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxyC_{1-4}alkyl, cyano, carboxyl, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, aryl;

r and s are each independently 0, 1, 2, 3, 4 or 5;

t is 0, 1, 2 or 3;

each R^1 and R^2 are independently hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)amino, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, aryl, arylC_{1-6}alkyl, aryloxy or arylC_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminocarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl; or

two R^1 or R^2 substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula

$-O-CH_2-O-$ (a-1),

$-O-CH_2-CH_2-O-$ (a-2),

$-O=CH=CH-$ (a-3),

$-O-CH_2-CH_2-$ (a-4),

$-O-CH_2-CH_2-CH_2-$ (a-5), or

$-CH=CH-CH=CH-$ (a-6);

R^3 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonyl, hydroxycarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, aryl, arylC_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

or a radical of formula

$-O-R^{10}$ (b-1),

$-S-R^{10}$ (b-2),

$-NR^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl, arylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, aryl, hydroxy, amino, C_{1-6}alkyloxy, C_{1-6}alkylcarbonylC_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC_{1-6}alkylcarbonyl, arylC_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, mono- or di(C_{1-6}alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C_{1-3}alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, or a radical or formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

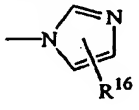
wherein Alk is C_{1-6}alkanediyl;

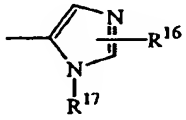
R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl or arylC_{1-6}alkyl;

R^4 is a radical of formula

 (c-1),

 (c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{16} may also be bound to one of the nitrogen atoms in the imidazole ring of formula (c-1) or (c-2), in which case the meaning of R^{16} when bound to the nitrogen is limited to hydrogen, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, arylC_{1-6}alkyl, trifluoromethyl or di(C_{1-4}alkyl)aminosulfonyl;

R^5 is C_{1-6}alkyl , C_{1-6}alkyloxy or halo;

aryl is phenyl, naphthalenyl or phenyl substituted with 1 or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by estrogen. Antiestrogen agents have therefore been proposed and used for the treatment of cancers especially breast cancer. One of the most widely used of such agents is tamoxifen which is a competitive inhibitor of estradiol binding to the estrogen receptor (ER). When bound to the ER, tamoxifen induces a change in the three-dimensional shape of the receptor, inhibiting its binding to the estrogen responsive element (ERE) on DNA. Under normal physiological conditions, estrogen stimulation increases tumor cell production of transforming growth cell b (TGF-b), an autocrine inhibitor of tumor cell growth. By blocking these pathways, the net effect of tamoxifen treatment is to decrease the autocrine stimulation of breast cancer growth. In addition, tamoxifen decreases the local production of insulin-like growth factor (IGF-1) by surrounding tissues: IGF-1 is a paracrine growth factor for the breast cancer cell (Jordan and Murphy, Endocr. Rev., 1990, 11; 578-610). Tamoxifen is the endocrine treatment of choice for post-menopausal women with metastatic breast cancer or at a high risk of recurrences from the disease. Tamoxifen is also used in pre-menopausal women with ER-positive tumors. There are various potential side-effects of long-term tamoxifen treatment for example the possibility of endometrial cancer and the occurrence of thrombo-embolic events. Thus, although tamoxifen has been widely used as a chemotherapeutic agent in humans, it is not therapeutically effective in all patients or against all types of tumors. Other estrogen receptor antagonists or selective estrogen receptor modulators include toremifene, droloxifene, faslodex and raloxifene.

In postmenopausal women, the principal source of circulating estrogen is from conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) by the aromatase enzyme in peripheral tissues. Estrogen deprivation through aromatase inhibition or inactivation is an effective and selective treatment for some postmenopausal patients with hormone-dependent breast cancer. Examples of aromatase inhibitors or inactivators include exemestane, anastrozole, letrazole and vorozole.

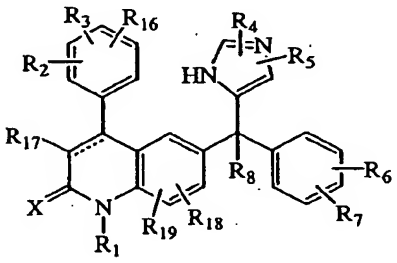
The term "antiestrogen agent" is used herein to include not only estrogen receptor antagonists and selective estrogen receptor modulators but also aromatase inhibitors as discussed above.

WO-01/45740 describes compositions and methods for treating and/or preventing breast cancer including compositions comprising at least one selective estrogen receptor modulator for example tamoxifen and at least one farnesyl transferase inhibitor for example FTI-277.

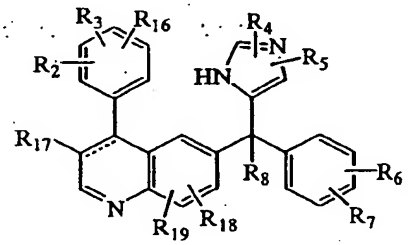
There is a need to increase the inhibitory efficacy of antiestrogen agents against tumor growth and also to provide a means for the use of lower dosages of such agents to reduce the potential of adverse toxic side effects to the patient.

It is an object of the invention to provide a therapeutic combination of an antiestrogen agent and a farnesyl transferase inhibitor of the type described above which has an advantageous inhibitory effect against tumor cell growth, in comparison with the respective effects shown by the individual components of the combination.

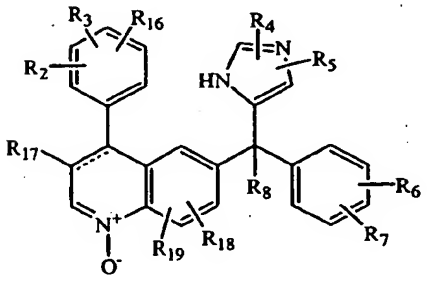
According to the invention therefore we provide a combination of an antiestrogen agent and a farnesyl transferase inhibitor of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) above, in particular a compound of formula (I), (II) or (III):



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9, wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl , C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkyl$S(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or

when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1), or

-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, or a radical of formula

-O-R^{10} (b-1),

-S-R^{10} (b-2),

-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{19} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.

In Formulas (I), (II) and (III), R^4 or R^5 may also be bound to one of the nitrogen atoms in the imidazole ring. In that case the hydrogen on the nitrogen is replaced by R^4 or R^5 and the meaning of R^4 and R^5 when bound to the nitrogen is limited to hydrogen, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl, C_{1-6}alkylS(O)$_2C_{1-6}$alkyl.

Preferably the substituent R^{18} is situated on the 5 or 7 position of the quinolinone moiety and substituent R^{19} is situated on the 8 position when R^{18} is on the 7-position.

Interesting compounds are these compounds of formula (I) wherein X is oxygen.

Also interesting compounds are these compounds of formula (I) wherein the dotted line represents a bond, so as to form a double bond.

Another group of interesting compounds are those compounds of formula (I) wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, wherein Alk^1 is methylene and R^9 is C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl.

Still another group of interesting compounds are those compounds of formula (I) wherein R^3 is hydrogen or halo; and R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy, trihalomethoxy or hydroxyC_{1-6}alkyloxy.

A further group of interesting compounds are those compounds of formula (I) wherein R^2 and R^3 are on adjacent positions and taken together to form a bivalent radical of formula (a-1), (a-2) or (a-3).

A still further group of interesting compounds are those compounds of formula (I) wherein R^5 is hydrogen and R^4 is hydrogen or C_{1-6}alkyl.

Yet another group of interesting compounds are those compounds of formula (I) wherein R^7 is hydrogen; and R^6 is C_{1-6}alkyl or halo, preferably chloro, especially 4-chloro.

A particular group of compounds are those compounds of formula (I) wherein R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, imidazolyl, or a radical of formula -$NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, or a radical of formula -Alk^2-OR^{13} wherein R^{13} is hydrogen or C_{1-6}alkyl.

Preferred compounds are those compounds wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, wherein Alk^1 is methylene and R^9 is C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl; R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy,

trihalomethoxy, hydroxyC_{1-6}alkyloxy or Ar^1; R^3 is hydrogen; R^4 is methyl bound to the nitrogen in 3-position of the imidazole; R^5 is hydrogen; R^6 is chloro; R^7 is hydrogen; R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, imidazolyl, or a radical of formula -$NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, or a radical of formula -Alk^2-OR^{13} wherein R^{13} is C_{1-6}alkyl; R^{17} is hydrogen and R^{18} is hydrogen.

Most preferred compounds of formula (I) are
4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-2(1*H*)-quinolinone,
6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride.monohydrate;
6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone,
6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt; and
(+)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (Compound 75 in Table 1 of the Experimental part of WO-97/21701) ; or a pharmaceutically acceptable acid addition salt thereof. The latter compound is especially preferred.

Further preferred embodiments of the present invention include compounds of formula (IX) wherein one or more of the following restrictions apply:

- $=X^1$-X^2-X^3 is a trivalent radical of formula (x-1), (x-2), (x-3), (x-4) or (x-9) wherein each R^6 independently is hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, amino or aryl and R^7 is hydrogen;
- $>Y^1$-Y^2- is a trivalent radical of formula (y-1), (y-2), (y-3), or (y-4) wherein each R^9 independently is hydrogen, halo, carboxyl, C_{1-4}alkyl or C_{1-4}alkyloxycarbonyl;
- r is 0, 1 or 2;
- s is 0 or 1;
- t is 0;

- R^1 is halo, C_{1-6}alkyl or two R^1 substituents ortho to one another on the phenyl ring may independently form together a bivalent radical of formula (a-1);
- R^2 is halo;
- R^3 is halo or a radical of formula (b-1) or (b-3) wherein
  R^{10} is hydrogen or a radical of formula -Alk-OR^{13}.
  R^{11} is hydrogen;
  R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy or mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl;
  Alk is C_{1-6}alkanediyl and R^{13} is hydrogen;
- R^4 is a radical of formula (c-1) or (c-2) wherein
  R^{16} is hydrogen, halo or mono- or di(C_{1-4}alkyl)amino;
  R^{17} is hydrogen or C_{1-6}alkyl;
- aryl is phenyl.

A particular group of compounds consists of those compounds of formula (IX) wherein $=X^1$-X^2-X^3 is a trivalent radical of formula (x-1), (x-2), (x-3), (x-4) or (x-9), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r is 0 or 1, s is 1, t is 0, R^1 is halo, $C_{(1-4)}$alkyl or forms a bivalent radical of formula (a-1), R^2 is halo or C_{1-4}alkyl, R^3 is hydrogen or a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-1) or (c-2), R^6 is hydrogen, C_{1-4}alkyl or phenyl, R^7 is hydrogen, R^9 is hydrogen or C_{1-4}alkyl, R^{10} is hydrogen or -Alk-OR^{13}, R^{11} is hydrogen and R^{12} is hydrogen or C_{1-6}alkylcarbonyl and R^{13} is hydrogen;

Preferred compounds are those compounds of formula (IX) wherein $=X^1$-X^2-X^3 is a trivalent radical of formula (x-1) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-4), r is 0 or 1, s is 1, t is 0, R^1 is halo, preferably chloro and most preferably 3-chloro, R^2 is halo, preferably 4-chloro or 4-fluoro, R^3 is hydrogen or a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-1) or (c-2), R^6 is hydrogen, R^7 is hydrogen, R^9 is hydrogen, R^{10} is hydrogen, R^{11} is hydrogen and R^{12} is hydrogen;

Other preferred compounds are those compounds of formula (IX) wherein $=X^1$-X^2-X^3 is a trivalent radical of formula (x-2), (x-3) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r and s are 1, t is 0, R^1 is halo, preferably chloro, and most preferably 3-chloro or R^1 is C_{1-4}alkyl, preferably 3-methyl, R^2 is halo, preferably chloro, and most preferably 4-chloro, R^3 is a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-2), R^6 is C_{1-4}alkyl, R^9 is hydrogen, R^{10} and R^{11} are hydrogen and R^{12} is hydrogen or hydroxy.

The most preferred compounds of formula (IX) are
7-[(4-fluorophenyl)(1*H*-imidazol-1-yl)methyl]-5-phenylimidazo[1,2-a]quinoline;
α-(4-chlorophenyl)-α-(1-methyl-1*H*-imidazol-5-yl)-5-phenylimidazo[1,2-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1*H*-imidazol-5-yl)-imidazo[1,2-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1*H*-imidazol-5-yl)tetrazolo[1,5-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-1-methyl-α-(1-methyl-1H-imidazol-5-yl)-1,2,4-triazolo[4,3-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1*H*-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-4,5-dihydro-α-(1-methyl-1*H*-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1*H*-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-N-hydroxy-α-(1-methyl-1*H*-imidazol-5-yl)tetrahydro[1,5-a]quinoline-7-methanamine;
α-(4-chlorophenyl)-α-(1-methyl-1*H*-imidazol-5-yl)-5-(3-methylphenyl)tetrazolo[1,5-a]quinoline-7-methanamine; the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof.

5-(3-chlorophenyl)- α-(4-chlorophenyl)- α-(1-methyl-1*H*-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine, especially the (-) enantiomer, and its pharmaceutically acceptable acid addition salts are especially preferred.

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C_{1-6}alkyl defines straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl and the like; C_{1-8}alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C_{1-6}alkyl as well as the higher homologues thereof containing 7 or 8 carbon atoms such as, for example heptyl or

octyl; C_{1-12}alkyl again encompasses C_{1-8}alkyl and the higher homologues thereof containing 9 to 12 carbon atoms, such as, for example, nonyl, decyl, undecyl, dodecyl; C_{1-16}alkyl again encompasses C_{1-12}alkyl and the higher homologues thereof containing 13 to 16 carbon atoms, such as, for example, tridecyl, tetradecyl, pentedecyl and hexadecyl; C_{2-6}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; C_{1-6}alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof. The term "C(=O)" refers to a carbonyl group, "S(O)" refers to a sulfoxide and "$S(O)_2$" to a sulfon. The term "natural amino acid" refers to a natural amino acid that is bound via a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of the amino acid and the amino group of the remainder of the molecule. Examples of natural amino acids are glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylanaline, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine and histidine.

The pharmaceutically acceptable acid or base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and non-toxic base addition salt forms which the compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) are able to form. The compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid form with a suitable organic or inorganic base. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium

salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The terms acid or base addition salt also comprise the hydrates and the solvent addition forms which the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term stereochemically isomeric forms of compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some of the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX)" is meant to include also the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms.

A particularly preferred antiestrogen agent for use in accordance with the invention is tamoxifen. Tamoxifen is commercially available for example from AstraZeneca plc under the trade name Nolvadex and may be prepared for example as described in GB Patent Specifications 1064629 and 1354939 or by processes analogous thereto. Other antiestrogen agents include faslodex commercially available for example from AstraZeneca plc under the trade name Fulvestrant, raloxifene commercially available

for example from Eli Lilly under the trade name Evista, toremifene commercially available for example from Schering Corporation under the trade name Fareston, and the tamoxifen analog droloxifene. Aromatase inhibitors include letrazole, anastrozole commercially available for example from AstraZeneca plc under the trade name Arimidex, exemestane commercially available for example from Pharmacia & Upjohn under the trade name under the trade name Aromasin, and vorozole.

The present invention also relates to combinations according to the invention for use in medical therapy for example for inhibiting the growth of tumor cells.

The present invention also relates to the use of combinations according to the invention for the preparation of a pharmaceutical composition for inhibiting the growth of tumor cells.

The present invention also relates to a method of inhibiting the growth of tumor cells in a human subject which comprises administering to the subject an effective amount of a combination according to the invention.

This invention further provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a combination according to the invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g. loss of contact inhibition). This includes the abnormal growth of : (1) tumor cells (tumors) expressing an activated *ras* oncogene; (2) tumor cells in which the *ras* protein is activated as a result of oncogenic mutation of another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant *ras* activation occurs. Furthermore, it has been suggested in literature that *ras* oncogenes not only contribute to the growth of of tumors *in vivo* by a direct effect on tumor cell growth but also indirectly, *i.e.* by facilitating tumor-induced angiogenesis (Rak. J. et al, *Cancer Research*, 55, 4575-4580, 1995). Hence, pharmacologically targetting mutant *ras* oncogenes could conceivably suppress solid tumor growth *in vivo*, in part, by inhibiting tumor-induced angiogenesis.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of a combination according to the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated *ras* oncogene by the administration of an effective amount of combination

according to the present invention. The present invention is particularly applicable to the treatment of breast cancer including the advanced disease. Examples of other tumors which may be inhibited include, but are not limited to, lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumor of the skin (e.g. keratoacanthomas), kidney carninoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

This invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein *ras* proteins are aberrantly activated as a result of oncogenic mutation in genes, i.e. the *ras* gene itself is not activated by mutation to an oncogenic mutation to an oncogenic form, with said inhibition being accomplished by the administration of an effective amount of a combination according to the invention, to a subject in need of such a treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which *ras* is activated due to mutation or overexpression of tyrosine kinase oncogenes may be inhibited by the combinations according to the invention.

The antiestrogen agent and the farnesyl transferase inhibitor may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular antiestrogen agent and the farnesyl transferase inhibitor being administered, the route of administration of the combination, the particular tumor being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The farnesyl transferase inhibitor is advantageously administered in an effective amount of from 0.0001 mg/kg to 100 mg/kg body weight, and in particular from 0.001 mg/kg to 10 mg/kg body weight. More particularly, for an adult patient, the dosage is conveniently in the range of 50 to 500mg bid, advantageously 100 to 400 mg bid and particularly 300mg bid.

The antiestrogen agent is advantageously administered in a dosage of about 1 to 100mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60mg once a day. Exemestane is advantageously administered orally in a dosage of about 25mg once a day.

It is especially preferred to administer the farnesyl tranferase inhibitor at a dosage of 100 or 200mg bid for 7, 14, 21 or 28 days with a dosage of the antiestrogen agent in the ranges indicated above.

In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the antiestrogen agent and the farnesyl transferase inhibitor may be formulated into various pharmaceutical forms for administration purposes. The components may be formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing both components. Farnesyl protein transferase inhibitors can be prepared and formulated into pharmaceutical compositions by methods known in the art and in particular according to the methods described in the published patent specifications mentioned herein and incorporated by reference; for the compounds of formulae (I), (II) and (III) suitable examples can be found in WO-97/21701. Compounds of formulae (IV), (V), and (VI) can be prepared and formulated using methods described in WO 97/16443, compounds of formulae (VII) and (VIII) according to methods described in WO 98/40383 and WO 98/49157 and compounds of formula (IX) according to methods described in WO 00/39082 respectively.

The present invention therefore also relates to a pharmaceutical composition comprising an antiestrogen agent and a farnesyl tranferase inhibitor of formula (I) together with one or more pharmaceutical carriers. To prepare pharmaceutical compositions for use in accordance with the invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets,

wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

It may be appropriate to administer the required dose of each component of the combination as two, three, four or more sub-doses at appropriate intervals throughout the course of treatment. The sub-doses may be formulated as unit dosage forms, for example, in each case containing independently 0.01 to 500 mg, for example 0.1 to 200 mg and in particular 1 to 100mg of each active ingredient per unit dosage form.

Anti-tumor Activity of a Combination of a Farnesyl Transferase Inhibitor and an Anti-estrogen Agent

A combination of a farnesyl transferase inhibitor, namely the compound identified as Compound 75 above (R115777), and an anti-estrogen agent, namely tamoxifen (TMX), was tested for anti-tumor activity in comparison with the activity of the individual components of the combination, as described below.

Mice/Husbandry

Female Nude-Homo NCRNU non-ovarectimized mice 8 weeks of age were fed ad libitum water and an irradiated standard rodent diet. Mice were housed in stable microisolators on a 12 hour light cycle at 21-22° C and 40-60 % humidity.

Tumors

Mice were inoculated subcutaneously with 1×10^7 MCF7 human breast carcinoma cells in the flank. Tumors were monitored initially twice a week and then daily as neoplasms reached the desired size, approximately 100mg. When the carcinomas reached a size between 62-144 mg in calculated tumor weight, the animals were pair matched into the various treatment groups (group mean tumor weights ranged from 83-85mg).

Estimated tumor weight was calculated using the formula:

$$\text{Tumor Weight (mg)} = \frac{w^2 \times l}{2}$$

w= width and l=length in mm of a MCF7 tumor

Estrogen pellets (0.36 mg: α-estradiol, 60 day release) were implanted s.c. in the dorsal region of each mouse two days prior to MCF7 cell inoculation. Fresh estrogen pellets were implanted 64 days after the original implant. On Day 1 the estrogen pellets were

removed from the two groups administered Tamoxifen (Groups 3 and 5). The pellets were left in place in Groups 1, 2 and 4, and new estrogen pellets were implanted in mice in Groups 1,2 and 4 on Day 62 of the experiment. The old pellets were not removed from these groups at the time of replacement. The MCF7 breast tumor xenograft requires exogenous estrogen to be supplied to host mice to support the progressive growth of this carcinoma.

Drugs

The vehicle was 20% beta-cyclodextrin in 0.1N HCl. Beta-cyclodextrin was added slowly to a constantly stirred approximate volume of 0.1 N HCl to yield a 40% beta-cyclodextrin solution. The mixture was covered with foil and stirred until completely dissolved (several hours). The solution was then brought to final volume and filtered (0.2μm).

R115777 was dissolved in batches sufficient for seven days dosing at a time. R115777 was pulse sonicated for 10 minutes at 4°C, filtered (0.2µm) and transferred to sterile 15 or 50ml vials. This solution was further diluted using 20% beta-dextrin in 0.1 N HCl for lower concentration dose groups. Vials were wrapped in foil and stored at 4°C. The dosing volume (0.2ml/20g mouse) was weight adjusted.

Tamoxifen was reconstituted in corn oil at 10mg/ml. Dosing was not body weight adjusted; each mouse received 100 μL of the solution (1mg/mouse).

Treatment Plan

MCF-bearing nude mice were pair-matched on Day1 into five groups of twelve animals each. Tamoxifen was given s.c. at a dose of 1mg/mouse qd to end. R115777 was administered orally at 100mg/kg qd to end. The combination therapy group used the same regimens as were employed in the Tamoxifen and R115777 monotherapy groups. A growth control (no treatment group) and a vehicle control group were included in the study. Estrogen pellets were removed from the Tamoxifen monotherapy and the combination therapy groups on Day1, to avoid antagonizing the Tamoxifen antiestrogen effect

End point

The tumor growth inhibition (TGI) endpoint was used in this study to assess the efficacy of the various treatments. The tumor burden endpoint was set at 1.0g as measured by calliper. TGI values were determined on the last day of the study (Day 5), when all mice were under test, except those that had expired from treatment-related or

procedural causes. The mice were euthanized at termination, their MCF7 tumors were excised and weighed, and the TGI values were calculated from the final group mean carcinoma actual weights (excluding those that underwent tumor shrinkage; CRs or PRs).

At excision, tumors smaller than their size on Day 1 were called PRs (partial regressions), and a mouse with no visible carcinoma was termed a CR (complete regression).

Animals recorded as CRs or PRs were not included in the TGI calculations. The following formula was used to calculate the TGI values:

$$\%TGI = \left[1 - \left(\frac{\text{Mean Net Tumor Weight}_{\text{Treated}}}{\text{Mean Net Tumor Weight}_{\text{Control}}}\right)\right] \times 100\%$$

Sample Collection

At endpoint, tumors were removed and weighed. At their endpoint, after Day 27, each tumor was cut in half with a scalpel and half was placed in fifteen to twenty volumes of 10% neutral buffered formalin. The other half was snap-frozen in liquid nitrogen and stored at -80°C. At their endpoint, after Day 30, blood was collected from the remaining mice of Groups 3, 4 and 5 by cardiac puncture under CO_2 anesthesia. Serum was recovered, and stored at –80°C until the end of the study.

Results

SUMMARY OF REGRESSION OBSERVED IN ESTABLISHED MCF-7 HUMAN BREAST TUMOR XENOGRAFTS

Treatment:	TMX 1 mg/kg	R115777 100 mg/kg	TMX + R115777
Regression in Individual Animals*	10%	93%	94%
	78%	100%	94%
	94%		78%
	44%		95%
	59%		88%
	31%		31%
			100%

* Values indicate the magnitude of tumor regression expressed as % reduction from pretreatment tumor size Untreated control tumors showed no incidence of regression.

These data show that the tested combination unexpectedly increases cytotoxic tumor regression in comparison to the cytostatic effect of the individual components of the combination.

TABLE 1

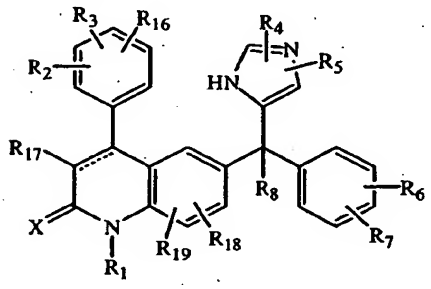
Protocol Design For The MCF7 Study

5

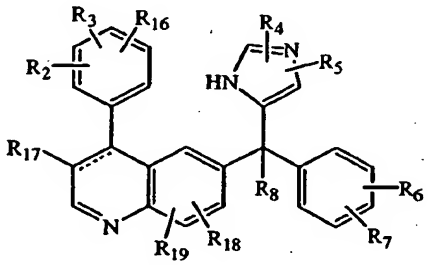
Group	n	Treatment Regimen 1				Treatment Regimen 2			
		Agent	mg/kg	Route	Schedule	Agent	mg/kg	Route	Schedule
1	12	Growth Control							
2	12	Vehicle		po	QD to end				
3	12	Tamoxifen	1 mg/mouse	sc	Qod to end				
4	12	R115777	100	po	QD to end				
5	12	Tamoxifen	1 mg/mouse	sc	Qod to end	R115777	100	po	Qd to end

Claims

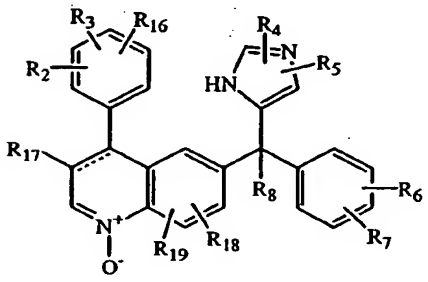
1. A combination of an antiestrogen agent and a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) below:



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,

or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9, wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyl-oxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy,

Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or

when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1), or

-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, or a radical of formula

-O-R^{10} (b-1),

-S-R^{10} (b-2),

-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino,

C_{1-6}alkylcarbonylamino, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

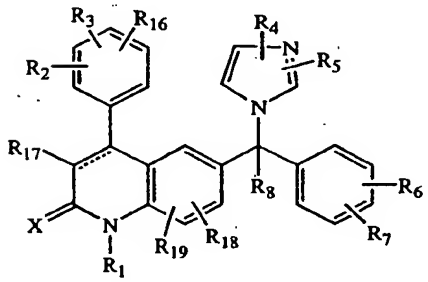
R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

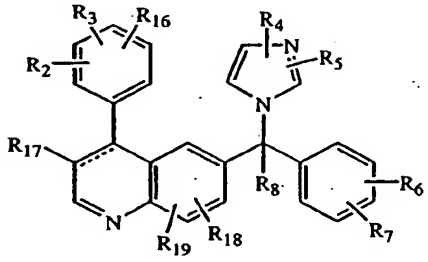
R^{19} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

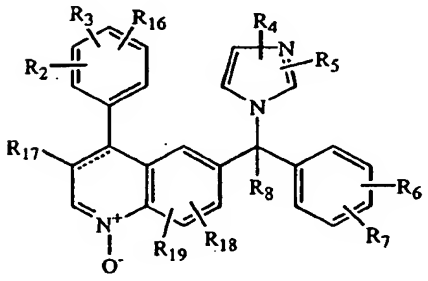
Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.



(IV)



(V)



(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,

or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9,

wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, amino-C_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, Ar^1, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkyl$S(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy or Ar^2oxy;

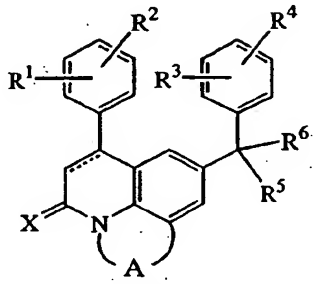
R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxycarbonylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, Ar^1, Ar^2C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl;

R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{11} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo;

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.



(VII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

-A- is a bivalent radical of formula

-CH=CH-	(a-1),	$-CH_2$-S-	(a-6),
$-CH_2-CH_2$-	(a-2),	$-CH_2-CH_2$-S-	(a-7),
$-CH_2-CH_2-CH_2$-	(a-3),	-CH=N-	(a-8),
$-CH_2$-O-	(a-4),	-N=N-	(a-9), or
$-CH_2-CH_2$-O-	(a-5),	-CO-NH-	(a-10);

wherein optionally one hydrogen atom may be replaced by C_{1-4}alkyl or Ar^1;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^2, Ar^2-C_{1-6}alkyl, Ar^2-oxy, Ar^2-C_{1-6}alkyloxy; or when on adjacent positions R^1 and R^2 taken together may form a bivalent radical of formula

$-O-CH_2-O-$	(b-1),
$-O-CH_2-CH_2-O-$	(b-2),
-O-CH=CH-	(b-3),
$-O-CH_2-CH_2-$	(b-4),
$-O-CH_2-CH_2-CH_2-$	(b-5), or
-CH=CH-CH=CH-	(b-6);

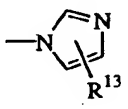
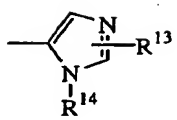
R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^3-oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R^3 and R^4 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1),

-O-CH_2-CH_2-O- (c-2), or

-CH=CH-CH=CH- (c-3);

R^5 is a radical of formula

 (d-1),  (d-2),

wherein R^{13} is hydrogen, halo, Ar^4, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxy-carbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{14} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^6 is hydrogen, hydroxy, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^5, Ar^5-C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^7 (e-1),

-S-R^7 (e-2),

-N-R^8R^9 (e-3),

wherein R^7 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^6, Ar^6-C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

R^8 is hydrogen, C_{1-6}alkyl, Ar^7 or Ar^7-C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^8, Ar^8-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^8-carbonyl, Ar^8-C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

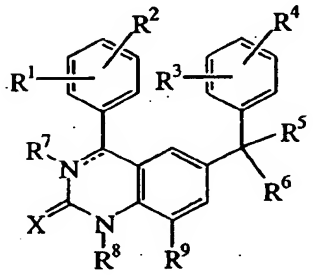
wherein Alk is C_{1-6}alkanediyl;

R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^9 or Ar^9-C_{1-6}alkyl;

R^{11} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^{10} or Ar^{10}-C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, Ar^{11} or Ar^{11}-C_{1-6}alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.



(VIII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^1C_{1-6}alkyl, Ar^1oxy or Ar^1C_{1-6}alkyloxy;

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl or trihalomethoxy;

R^5 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^{10} (a-1),

-S-R^{10} (a-2),

-N-$R^{11}R^{12}$ (a-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^1carbonyl, Ar^1C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino,

or a radical or formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

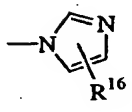
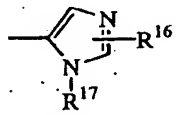
wherein Alk is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^6 is a radical of formula

 (b-1),  (b-2),

wherein R^{16} is hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^7 is hydrogen or C_{1-6}alkyl provided that the dotted line does not represent a bond;

R^8 is hydrogen, C_{1-6}alkyl or Ar^2CH_2 or Het^1CH_2;

R^9 is hydrogen, C_{1-6}alkyl , C_{1-6}alkyloxy or halo; or

R^8 and R^9 taken together to form a bivalent radical of formula

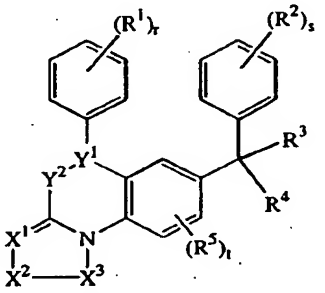
-CH=CH- (c-1),
-CH_2-CH_2- (c-2),
-CH_2-CH_2-CH_2- (c-3),
-CH_2-O- (c-4), or
-CH_2-CH_2-O- (c-5);

Ar^1 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl;

Ar^2 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl; and

Het^1 is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl

and



(IX)

or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$=X^1-X^2-X^3-$ is a trivalent radical of formula

$=N-CR^6=CR^7-$	(x-1),	$=CR^6-CR^7=CR^8-$	(x-6),
$=N-N=CR^6-$	(x-2),	$=CR^6-N=CR^7-$	(x-7),
$=N-NH-C(=O)-$	(x-3),	$=CR^6-NH-C(=O)-$	(x-8), or
$=N-N=N-$	(x-4),	$=CR^6-N=N-$	(x-9);
$=N-CR^6=N-$	(x-5),		

wherein each R^6, R^7 and R^8 are independently hydrogen, C_{1-4}alkyl, hydroxy, C_{1-4}alkyloxy, aryloxy, C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, cyano, amino, thio, C_{1-4}alkylthio, arylthio or aryl;

$>Y^1-Y^2-$ is a trivalent radical of formula

$>CH-CHR^9-$	(y-1),	
$>C=N-$	(y-2),	
$>CH-NR^9-$	(y-3),or	
$>C=CR^9-$	(y-4);	

wherein each R^9 independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxyC_{1-4}alkyl, cyano, carboxyl, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, aryl;

r and s are each independently 0, 1, 2, 3, 4 or 5;

t is 0, 1, 2 or 3;

each R^1 and R^2 are independently hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or

di(C_{1-6}alkyl)amino, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, aryl, arylC_{1-6}alkyl, aryloxy or arylC_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminocarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl; or

two R^1 or R^2 substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O=CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2- CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^3 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonyl, hydroxycarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, aryl, arylC_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

or a radical of formula

-O-R^{10} (b-1),

-S-R^{10} (b-2),

-N$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl, arylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-N$R^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, aryl, hydroxy, amino, C_{1-6}alkyloxy, C_{1-6}alkylcarbonylC_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC_{1-6}alkylcarbonyl, arylC_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, mono- or di(C_{1-6}alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C_{1-3}alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, or a radical or formula -Alk-OR^{13} or -Alk-N$R^{14}R^{15}$;

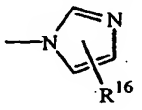
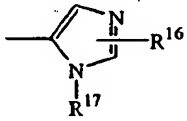
wherein Alk is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl or arylC_{1-6}alkyl;

R^4 is a radical of formula

 (c-1),  (c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{16} may also be bound to one of the nitrogen atoms in the imidazole ring of formula (c-1) or (c-2), in which case the meaning of R^{16} when bound to the nitrogen is limited to hydrogen, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, arylC_{1-6}alkyl, trifluoromethyl or di(C_{1-4}alkyl)aminosulfonyl;

R^5 is C_{1-6}alkyl , C_{1-6}alkyloxy or halo;

aryl is phenyl, naphthalenyl or phenyl substituted with 1 or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

2. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein X is oxygen and the dotted line represents a bond.

3. A combination as claimed in claim 1 or claim 2 wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl or mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl and wherein R^3 is hydrogen and R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy, trihalomethoxy or hydroxyC_{1-6}alkyloxy.

4. A combination as claimed in any of the preceding claims wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, imidazolyl, or a radical of formula -$NR^{11}R^{12}$

wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, or a radical of formula -Alk^2-OR^{13} wherein R^{13} is hydrogen or C_{1-6}alkyl.

5. A combination as claimed in claim 1 wherein the farnesyl transferase inhibitor is selected from:
4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)-methyl]-1-methyl-2(1*H*)-quinolinone,
6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxy-phenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride.monohydrate;
6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxy-phenyl)-1-methyl-2(1*H*)-quinolinone, and
6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salts thereof.

6. A combination as claimed in claim 1 wherein the farnesyl transferase inhibitor is (+)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chloro-phenyl)-1-methyl-2(1*H*)-quinolinone; or a pharmaceutically acceptable acid addition salt thereof.

7. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is a compound of formula (IX) wherein =X^1-X^2-X^3 is a trivalent radical of formula (x-2), (x-3) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r and s are 1, t is 0, R^1 is halo, preferably chloro, and most preferably 3-chloro or R^1 is C_{1-4}alkyl, preferably 3-methyl, R^2 is halo, preferably chloro, and most preferably 4-chloro, R^3 is a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-2), R^6 is C_{1-4}alkyl, R^9 is hydrogen, R^{10} and R^{11} are hydrogen and R^{12} is hydrogen or hydroxy.

8. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is 5-(3-chlorophenyl)- α-(4-chlorophenyl)- α (1-methyl-1*H*-imidazol-5-

yl)tetrazolo[1,5-a]quinazoline-7-methanamine or a pharmaceutically acceptable acid addition salt thereof.

9. A combination as claimed in any of the preceding claims in which the antiestrogen agent is an estrogen receptor antagonist or a selective estrogen receptor modulator.

10. A combination as claimed in claim 9 in which the antiestrogen agent is tamoxifen.

11. A combination as claimed in claim 9 in which the antiestrogen agent is faslodex, raloxifene, toremifene or droloxifene.

12. A combination as claimed in any of claims 1 to 8 in which the antiestrogen agent is an aromatase inhibitor

13. A combination as claimed in claim 12 in which the antiestrogen agent is letrazole, anastrozole, exemestane or vorozole.

14. A combination as claimed in any of the preceding claims in the form of a pharmaceutical composition comprising an antiestrogen agent and a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) (as defined in claim 1) together with one or more pharmaceutical carriers.

15. A combination as claimed in any of the preceding claims for use in medical therapy.

16. A combination as claimed in claim15 for inhibiting the growth of tumor cells.

17. Use of a combination as claimed in any of claims 1 to 14 in the manufacture of a pharmaceutical composition for inhibiting the growth of tumor cells.

18. A method of inhibiting the growth of tumor cells in a human subject which comprises administering to the subject an effective amount of a combination as claimed in any of claims 1 to 14.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/01248

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/47 A61K31/505 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 32114 A (SCHERING CORP) 1 July 1999 (1999-07-01) claim 1 page 15	1-18
Y	WO 99 08682 A (UNIV DUKE) 25 February 1999 (1999-02-25) page 13 claim 8	1-18
Y	WO 97 16443 A (JANSSEN PHARMACEUTICA NV ;ANGIBAUD PATRICK RENE (FR); SANZ GERARD) 9 May 1997 (1997-05-09) . cited in the application claim 1	1-18

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2002	31/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/01248

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 49157 A (FREYNE EDDY JEAN EDGARD ;JANSSEN PHARMACEUTICA NV (BE); ANGIBAUD P) 5 November 1998 (1998-11-05) cited in the application claim 1	1-18
Y	WO 98 40383 A (JANSSEN PHARMACEUTICA NV ;ANGIBAUD PATRICK RENE (FR); LIGNY YANNIC) 17 September 1998 (1998-09-17) cited in the application claim 1	1-18
Y	WO 00 39082 A (JANSSEN PHARMACEUTICA NV ;ANGIBAUD PATRICK RENE (FR); VENET MARC G) 6 July 2000 (2000-07-06) cited in the application claim 1	1-18
X	WO 00 25789 A (OLIFF ALLEN I ;GIBBS JACKSON B (US); MERCK & CO INC (US)) 11 May 2000 (2000-05-11) page 80 claim 24	1-16
P,X	WO 01 56552 A (PALMER PETER ALBERT ;JANSSEN PHARMACEUTICA NV (BE); HORAK IVAN DAV) 9 August 2001 (2001-08-09) claim 12	1-18
P,X	WO 01 62234 A (JANSSEN PHARMACEUTICA NV ;END DAVID WILLIAM (US)) 30 August 2001 (2001-08-30) page 27	1-18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/01248

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9932114 A	01-07-1999	AU 1907299 A	12-07-1999
		BR 9814419 A	10-10-2000
		CA 2315693 A1	01-07-1999
		CN 1284875 T	21-02-2001
		EP 1041985 A1	11-10-2000
		JP 2001526224 T	18-12-2001
		NO 20003229 A	22-08-2000
		SK 8982000 A3	09-04-2001
		WO 9932114 A1	01-07-1999
		ZA 9811734 A	21-06-1999
WO 9908682 A	25-02-1999	AU 8906398 A	08-03-1999
		BR 9811946 A	22-08-2000
		CA 2301032 A1	25-02-1999
		CN 1275911 T	06-12-2000
		EE 200000077 A	15-12-2000
		EP 1019057 A1	19-07-2000
		HU 0002852 A2	28-10-2001
		JP 2001515038 T	18-09-2001
		NO 20000752 A	15-02-2000
		NZ 502738 A	28-06-2002
		PL 338555 A1	06-11-2000
		WO 9908682 A1	25-02-1999
WO 9716443 A	09-05-1997	AT 212627 T	15-02-2002
		AU 712435 B2	04-11-1999
		AU 7493396 A	22-05-1997
		CN 1200732 A	02-12-1998
		CZ 9801272 A3	16-12-1998
		DE 69618999 D1	14-03-2002
		DK 1019395 T3	06-05-2002
		EA 980395 A1	29-10-1998
		WO 9716443 A1	09-05-1997
		EP 1106610 A1	13-06-2001
		EP 1019395 A1	19-07-2000
		HU 9802424 A2	28-10-1999
		JP 11514635 T	14-12-1999
		NO 980928 A	29-04-1998
		NZ 321576 A	28-05-1999
		PL 328230 A1	18-01-1999
		SI 1019395 T1	30-06-2002
		SK 55698 A3	11-02-1999
		TR 9800720 T2	21-09-1998
		US 5968952 A	19-10-1999
		ZA 9609087 A	29-04-1998
WO 9849157 A	05-11-1998	AU 738628 B2	20-09-2001
		AU 7646098 A	24-11-1998
		BR 9809398 A	13-06-2000
		CN 1252800 T	10-05-2000
		WO 9849157 A1	05-11-1998
		EP 0977750 A1	09-02-2000
		HU 0001122 A2	28-04-2001
		JP 2001522364 T	13-11-2001
		NO 995169 A	27-12-1999
		NZ 336233 A	26-01-2001
		PL 336468 A1	19-06-2000
		SK 146199 A3	12-06-2000

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/01248

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9849157	A		TR	9902606 T2	21-07-2000
			US	6177432 B1	23-01-2001
			US	6358961 B1	19-03-2002
			ZA	9803504 A	25-10-1999
WO 9840383	A	17-09-1998	AU	7031898 A	29-09-1998
			BR	9808843 A	04-07-2000
			CN	1249753 T	05-04-2000
			WO	9840383 A1	17-09-1998
			EP	0970079 A1	12-01-2000
			HU	0001498 A2	28-11-2000
			JP	2001515487 T	18-09-2001
			NO	994268 A	08-11-1999
			NZ	336234 A	27-10-2000
			PL	335518 A1	25-04-2000
			SK	121799 A3	16-05-2000
			TR	9902203 T2	21-12-1999
			US	6187786 B1	13-02-2001
			US	2002049327 A1	25-04-2002
			ZA	9801978 A	09-09-1999
WO 0039082	A	06-07-2000	AU	2795300 A	31-07-2000
			BG	105631 A	28-02-2002
			BR	9916827 A	16-10-2001
			CN	1331693 T	16-01-2002
			CZ	20012142 A3	16-01-2002
			WO	0039082 A2	06-07-2000
			EP	1140935 A2	10-10-2001
			NO	20013088 A	21-06-2001
			TR	200101961 T2	21-12-2001
WO 0025789	A	11-05-2000	AU	1230100 A	22-05-2000
			WO	0025789 A1	11-05-2000
WO 0156552	A	09-08-2001	AU	3372601 A	14-08-2001
			WO	0156552 A2	09-08-2001
WO 0162234	A	30-08-2001	AU	3176301 A	03-09-2001
			WO	0162234 A2	30-08-2001

Form PCT/ISA/210 (patent family annex) (July 1992)